British Heart Journal, 1977, **39**, 866–871

Hypertensive pulmonary vascular disease in children
Detection by radioactive nitrogen (^{13}N) inhalation and injection

S. A. McKENZIE, C. G. C. MacARTHUR, S. GODFREY, AND K. A. HALLIDIE-SMITH

From Department of Paediatrics and Neonatal Medicine, and Department of Medicine (Clinical Cardiology), Hammersmith Hospital and Royal Postgraduate Medical School, London

Regional lung function has been studied in 16 children with intracardiac shunts and a variety of associated cardiac anomalies using radioactive nitrogen (^{13}N) and a gamma camera-computer system. The distribution and washout of inhaled ^{13}N were usually normal. The distribution of intravenously injected ^{13}N was often abnormal and could be related to local anatomy. The most important finding was delayed clearance by ventilation of intravenously injected ^{13}N in children with an abnormally raised pulmonary/systemic vascular resistance ratio (Rp/Rs) at cardiac catheterisation. The regional localisation of this ventilation-perfusion imbalance could be related in several children to the probable distribution of hypertensive pulmonary vascular disease, predicted either from local anatomy shown at cardiac catheterisation or from the abnormal distribution of pulmonary perfusion. Abnormalities present on breathing air may be partially reversed on breathing 100 per cent oxygen.

Hypertensive pulmonary vascular disease in children with congenital cardiac defects greatly influences operative risks (Cartmill *et al.*, 1966; Espino-Vela *et al.*, 1968), postoperative course (Park *et al.*, 1969), and long-term haemodynamic results (Braunwald *et al.*, 1962; Maron *et al.*, 1973; Allen *et al* 1974; Whitman and Ellis, 1975). Hypertensive pulmonary vascular disease is generally considered to be present when the pulmonary vascular resistance or the pulmonary: systemic resistance ratio (Rp/Rs) calculated at cardiac catheterisation is abnormally raised (Braunwald *et al.*, 1962; Kirklin, 1965; Allen *et al.*, 1974).

We have recently developed a free breathing technique for studying regional lung function in children of all ages using radioactive nitrogen (^{13}N) and a gamma camera (Godfrey *et al*, 1975; Ronchetti *et al.*, 1975) and have found a consistent pattern of abnormality in children with hypertensive pulmonary vascular disease. We present our observations on this phenomenon which could provide a simpler method for the detection and evaluation of pulmonary vascular disease.

Received for publication 25 November 1976

Subjects and methods

Sixteen children aged 7 months to 12 years were studied. Each had been referred for investigation of congenital heart disease and had undergone cardiac catheterisation. The anatomical diagnoses and cardiac catheterisation results are shown in Table 1. The pulmonary: systemic resistance ratio (Rp/Rs) was calculated by the standard technique (Grossman, 1974) using the pulmonary arteriolar resistance in the numerator. Pulmonary and systemic flows were derived by the Fick principle. Taking the upper normal limit for Rp/Rs as 0·25 (Kirklin 1965), cases 1 to 4 were considered not to have hypertensive pulmonary vascular disease. Most of the remaining patients had a raised Rp/Rs ratio indicative of hypertensive pulmonary vascular disease. Cases 15 and 16 had complex anatomy with a large systemic-pulmonary anastomosis supplying only part of the pulmonary vascular bed, precluding calculation of Rp/Rs, while case 7 had multiple peripheral pulmonary stenoses with a normal mean pulmonary arterial pressure distal to the stenosis in the right lower lobe. In cases 10 and 11,

Rp/Rs fell after inhalation of 100 per cent oxygen.

Regional lung function studies were performed as previously described (Ronchetti *et al.*, 1975), with the child lying supine over the gamma camera and breathing air spontaneously. Cases 6 and 10 were also studied while breathing 100 per cent oxygen. The younger children were lightly sedated with diazepam. ^{13}N was made by the Medical Research Council Cyclotron Unit and piped directly to the adjacent room for immediate use because of its short half-life (10 minutes). For the study of ventilation, a 4 ml bolus of the gas was delivered at end-expiration into the nasopharynx via an infant feeding tube or through a mouthpiece. For the study of pulmonary perfusion, a bolus of ^{13}N was dissolved in 4 ml isotopic saline and was injected rapidly via an indwelling needle into an arm vein. Because of the extreme insolubility of ^{13}N, virtually all the injected isotope reaching the pulmonary capillaries passed rapidly into alveoli and was then washed out by ventilation. During and after each administration of isotope the lungs were scanned continuously by a gamma camera for 5 to 10 minutes and the data stored on magnetic tape. Data processing was performed with the aid of a digital computer. For each study, an image of the counts over the lungs was displayed on an oscilloscope and each lung field was divided into an upper and lower zone using a light pen. Correction was made for camera uniformity, for background activity which included activity reaching the systemic circulation by right-to-left shunting, and for isotope decay. Activity time curves were plotted for each lung zone and indices of regional lung function calculated as described below.

Calculation of results

A distribution index (DI) for each zone for both ventilation and perfusion was calculated from the following equation:

$$DI = \frac{\text{Regional counts}}{\text{Whole lung counts}} \div \frac{\text{Regional area}}{\text{Whole lung area}}$$

Assuming that relative regional image areas reflect regional volumes, even distribution of ventilation or perfusion throughout the lungs would be denoted in each zone by a distribution index of 1·0 (Ronchetti *et al.*, 1975). This assumption is not always valid in children with cardiac disease since an enlarged heart may distort pulmonary anatomy. However, it is possible to derive an improved regional 'volume-corrected' perfusion distribution index in children with uniform regional ventilation. Since ventilation is then directly proportional to lung volume, the perfusion distribution index for each zone of the lung is the distribution index for that zone in the perfusion study, divided by the equivalent distribution index in the ventilation study. It is necessary for this index that the areas on the oscilloscope image for both studies should be identical.

For a better analysis of the washout curves independent of assumption about lung volumes, a transfer function (H/A) has been calculated by dividing the peak height (H) of the curve by the area (A) under the washout portion (Ronchetti *et al.*, 1975). In the inhalation study, H/A represents ventilation per unit lung volume (fractional ventilation) but in the study with injected ^{13}N it is a complex function of ventilation, perfusion, and lung volume (Winlove *et al.*, 1976). The washout curves from both studies would be identical if alveolar ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) were evenly matched. Any difference between the curves is, therefore, an index of ventilation/perfusion ($\dot{V}/\dot{Q}$) imbalance resulting from reduced $\dot{V}/\dot{Q}$ ratios (Fig 1). A normal range of H/A values has been obtained from studies of 20 normal lung zones in 10 children with localised lung disease (Winlove *et al.*, 1976). For ventilation, the mean H/A is 3·65 with a range (± 2 SD on a logarithmic scale) 2·23–6·08 and for perfusion it is 2·82 with a similar range 2·08–4·39. We have, therefore, taken 2·0 as the lower normal limit for H/A in both studies.

Table 1 *Patients studied, diagnoses, and Rp/Rs values*

Case No.	*Age (y)*	*Diagnosis*	*Rp/Rs*
1	4	VSD; peripheral pulmonary stenoses	0·06
2	6	Tetralogy of Fallot	0·09
3	4	VSD	0·10
4	2	VSD	0·22
5	14/12	VSD	0·32
6	3	VSD	0·45
7	3	VSD; peripheral pulmonary stenoses to all regions except right upper zone	0·54†
8	8	Total anomalous pulmonary venous drainage	0·61
9	6	VSD	0·63
10	7/12	Secundum ASD and VSD	0·75
			0·20*
11	5	VSD	0·76
			0·17*
12	15/12	Persistent ductus arteriosus	0·89
13	4	VSD	1·66
14	3	Primary pulmonary hypertension	2·55
15	3	Tetralogy of Fallot, Waterston shunt	Not calculable
16	12	Pulmonary atresia, Blalock-Taussig shunt; absent right pulmonary artery	Not calculable

*While breathing 100 per cent oxygen.
†Calculated using pulmonary arterial pressure proximal to the stenoses.
VSD, ventricular septal defect; ASD, atrial septal defect; Rp/Rs, pulmonary/systemic resistance ratio.

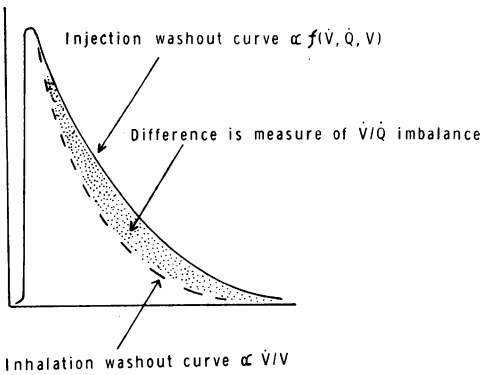

Fig. 1 *Schematic curves for washout of ^{13}N after injection and inhalation. $\dot{V}$, ventilation; $\dot{Q}$, perfusion; V, volume.*

Results

VENTILATION

As shown in Table 2, the fractional ventilation of inhaled ^{13}N was abnormal only in one zone of one child (case 4) and showed regional variation in one further child (case 15). Both children had previously undergone intrathoracic surgery. Fractional ventilation was not calculable for case 10 as data from the bolus inhalation were not available.

PERFUSION

Abnormalities of the washout (H/A) after injection of ^{13}N were present in several children and could be related both to the elevation of Rp/Rs and to regional anatomy. On the basis of these results, the children were divided into groups:

Group 1 (cases 1 to 4)
All values of H/A after injection and Rp/Rs were normal. Fig 2 shows the washout curves after both inhalation and injection of ^{13}N in case 3 and is typical of the group.

Group 2 (cases 5, 9, 10, 12, 13, 14, and 16)
In this group washout after injection was abnormally slow in at least 3 lung zones. Haemodynamic evidence for hypertensive pulmonary vascular disease was present in each patient except case 16, in whom calculation of Rp/Rs was not possible. The washout curves of case 12 are shown in Fig 3. In case 10 the changes were partially reversed while breathing 100 per cent oxygen.

Group 3 (cases 6, 7, 8, 11, and 15)
Local abnormalities of washout after injection were present in these patients and all had haemodynamic evidence of hypertensive pulmonary vascular disease. In cases 8 and 11 in whom the pulmonary vascular disease was thought to be early and reversible the abnormalities occurred in the regions of

Table 2 *Results of regional lung function studies*

Case No.	*Perfusion distribution index (PDI)*				*Fractional ventilation (H/A)*				*Washout after infusion (H/A)*			
	RU	*RL*	*LU*	*LL*	*RU*	*RL*	*LU*	*LL*	*RU*	*RL*	*LU*	*LL*
1	0·91	0·66	2·59	1·86	2·69	2·89	2·94	2·69	2·09	2·17	2·15	2·14
2	1·67	1·32	0·31	0·69	2·40	2·31	2·49	1·98	5·93	3·04	4·28	2·48
3	1·06	1·09	0·79	1·35	3·72	3·47	4·12	3·69	2·52	3·33	3·82	3·49
4	*	*	*	*	1·88	2·09	3·05	3·72	2·71	2·46	3·02	2·27
5	1·02	0·84	0·87	2·19	3·61	3·66	4·46	2·85	1·75	1·98	2·33	1·01
6	1·09	0·78	1·72	0·76	5·02	4·90	3·28	3·99	2·55	2·56	1·66	1·09
									2·67	3·22	2·03	1·34†
7	0·98	1·09	1·08	0·78	3·21	2·68	2·42	2·44	1·28	2·01	2·13	2·18
8	0·72	0·69	1·46	1·40	3·80	3·27	3·39	3·79	2·60	4·27	1·23	1·75
9	1·28	0·92	1·01	0·73	3·86	3·54	4·29	3·91	2·27	1·63	1·63	1·29
10	1·19	1·10	1·03	0·94	Not calculable				0·86	1·33	0·66	0·91
									1·28	2·44	1·14	1·65†
11	0·67	1·22	0·81	1·65	4·03	3·48	4·05	3·71	5·97	4·33	4·72	2·12
12	0·85	1·13	1·36	1·44	1·44	3·28	3·19	2·58	0·87	0·74	1·45	1·40
13	1·11	0·81	1·35	0·93	2·27	2·66	2·20	2·47	0·98	1·06	1·21	0·79
14	0·43	0·31	1·95	1·833	4·28	4·29	3·48	4·22		0·94		1·75
15	*	*	*	*	2·11	2·40	3·90	4·33	3·36	1·95	3·95	3·36
16	1·43	0·74	1·33	1·03	3·20	2·61	3·38	3·15	2·84	1·56	1·41	0·69

*Perfusion distribution index not calculable because of regional variation in fractional ventilation.
†While breathing 100 per cent oxygen.
RU, right upper zone; LU, left upper zone; RL, right lower zone; LL, left lower zone.

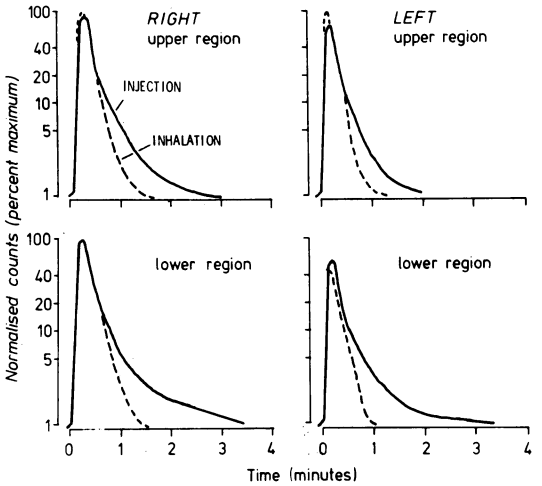

Fig. 2 *Washout curves for case 3 showing rapid washout of ^{13}N after both injection and inhalation.*

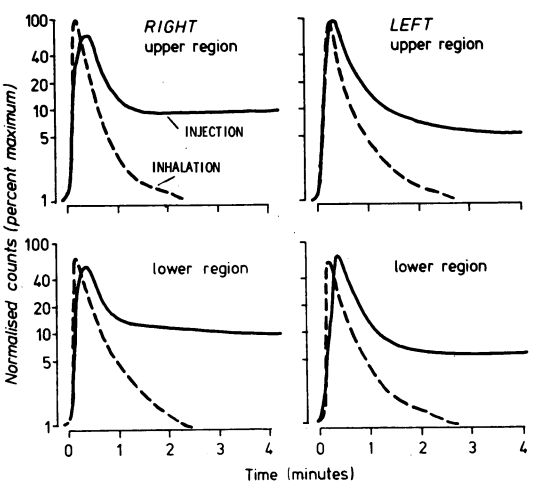

Fig. 3 *Washout curves for case 12 showing generalised delay in washout of ^{13}N after injection.*

greatest perfusion. Two patients had unusual anatomy and their abnormalities were restricted to areas either where there was no protective pulmonary stenosis (case 7) or where there was a large systemic-pulmonary shunt (case 15). In case 6 there was overall improvement in the washout curves after injection while breathing 100 per cent oxygen but washout in the left lower zone was still abnormally slow. Fig 4a shows the localised delay in washout in case 7 and Fig 4b is the pulmonary angiogram of the same patient showing stenoses of the left main pulmonary artery and the inferior branch of the right pulmonary artery.

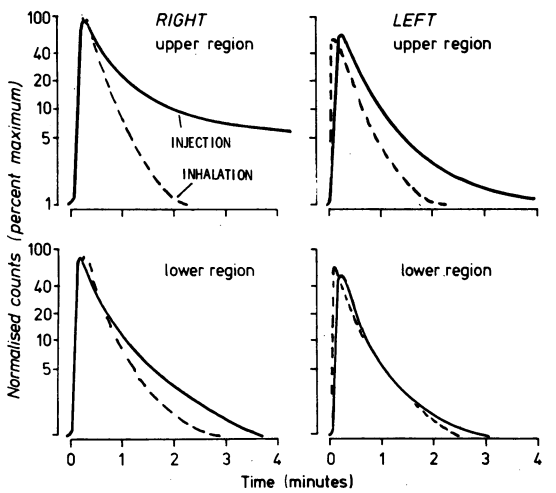

Fig. 4a *Washout curves for case 7 showing a localised delay in washout of ^{13}N after injection.*

Discussion

There appears to be a consistent pattern of abnormality in ^{13}N washout after intravenous injection in children with hypertensive pulmonary vascular disease. All patients in group 2, with the exception of case 16, had normal pulmonary artery anatomy and haemodynamic evidence of hypertensive pulmonary vascular disease. All had generalised delay

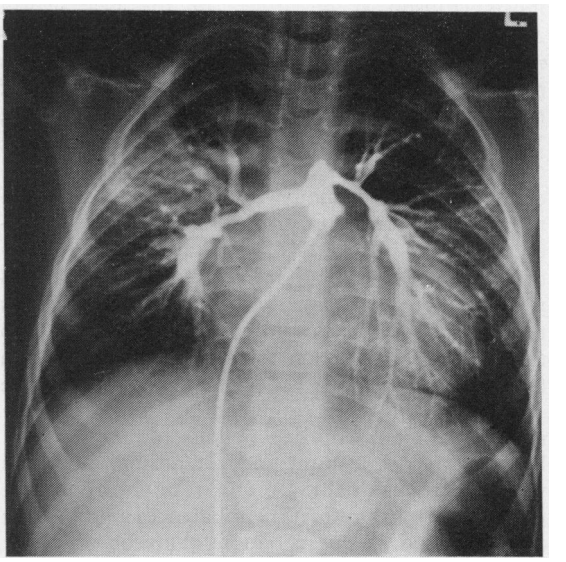

Fig. 4b *Pulmonary angiogram of case 7 showing hypoperfusion of the left lung and lower zone of the right lung.*

in washout after injection of ^{13}N. In contrast, those patients in group 3 with abnormal pulmonary artery anatomy had related localised abnormalities in washout. Though Rp/Rs could not be calculated in case 16, he would appear from this study to have hypertensive pulmonary vascular disease affecting mainly the left lung, the side of the Blalock-Taussig shunt. The flow to this lung was relatively low, indicating that the hypertensive pulmonary vascular disease was severe and flow-limiting. In this context it is interesting that Alderson *et al.* (1976) found diminished pulmonary perfusion on the side of the shunt in patients with previous shunt operations for tetralogy of Fallot. Their demonstration of relatively normal regional ventilation using ^{133}Xe scans is confirmed in this study and is shown to be true even in the presence of severe hypertensive pulmonary vascular disease.

The delay in clearance of ^{13}N in the injection study indicates that a proportion of the gas is entering perfused but extremely poorly ventilated alveoli. Such a $\dot{V}/\dot{Q}$ imbalance should produce systemic arterial desaturation, and this has been noted previously in patients with primary pulmonary hypertension (Wood, 1952). Several authors have investigated the causes of the increased alveolar-arterial oxygen gradient ((A–a) DO_2) in both children (Lees *et al.* (1967) and adults (Woolf, 1963; Wessel *et al.*, 1964) with intracardiac shunts or primary pulmonary hypertension. Studies in dogs with pulmonary hypertension caused either by surgically produced systemic-pulmonary anastomosis (Ellison *et al.*, 1961) or the heart-worm *Dirofilaria immitis* (Kentera *et al.*, 1965) have confirmed an increased (A–a) DO_2 whose severity is related to the pulmonary artery pressure. Several of these authors (Ellison *et al.*, 1961; Kentera *et al.*, 1965; Lees *et al.*, 1967) have concluded from the effects on (A–a) DO_2 of high inspired oxygen concentrations that venous admixture through pulmonary arteriovenous shunts rather than $\dot{V}\dot{Q}$ imbalance is the primary cause of the arterial desaturation. It is not possible to interpret our results in this manner, however, since venous admixture of this type would produce rapid removal of isotope into the systemic circulation with effective elimination from the record with background correction. The efficacy of this correction can be seen from the results of case 2 who had Fallot's tetralogy with a large right-to-left shunt and yet normal perfusion washout curves (Table 2). Our results can only be interpreted in terms of $\dot{V}/\dot{Q}$ imbalance; a proportion of the injected ^{13}N enters regions of alveoli which are so poorly ventilated that they do not contribute significantly to the fractional ventilation measured after inhalation of ^{13}N which, therefore, remains normal. These regions would probably not become completely oxygenated when breathing 100 per cent oxygen and hence would not have been considered as $\dot{V}/\dot{Q}$ imbalance in the previous studies (Ellison *et al.*, 1961; Kentera *et al.*, 1965; Lees *et al.*, 1967).

The physiological mechanisms underlying these observations remain a mystery so far but one tentative explanation might be a 'closing volume' type of effect whereby a substantial proportion of small airways are occluded for part of the respiratory cycle. This is known to occur, for example, when there is loss of elastic recoil as in emphysema. The alveoli supplied by such airways would receive intravenous ^{13}N but not inhaled ^{13}N and would cause the difference in the shape of the respective washout curves. The pathological mechanism responsible for such a phenomenon, or indeed for any other mechanism causing our observed $\dot{V}/\dot{Q}$ imbalance, is unknown. We know of no histological evidence for small airway obstruction and it is unlikely to be caused by oedema as this is not a feature of chronic pulmonary hypertension (Damman and Ferencz, 1956). Gradual improvement of (A–a) DO_2 in association with gradual reduction in pulmonary artery pressure has been shown in one dog after ligation of a systemic-pulmonary anastomosis (Ellison *et al.*, 1961). We have shown some acute improvement in ^{13}N washout after injection in cases 6 and 10 while breathing 100 per cent oxygen. In case 10, Rp/Rs was also reduced at cardiac catheterisation in response to 100 per cent oxygen but the implications of this and of other current attempts to determine closing volumes are as yet uncertain. It appears, therefore, that the $\dot{V}/\dot{Q}$ imbalance in this study can be associated with reversible pulmonary vascular disease.

Regional lung function studies using ^{13}N are easy to perform on children of all ages. The radiation dose (200–400 m.rads) is only a fraction of that received at cardiac catheterisation. There is, furthermore, the advantage over catheterisation that regional information is obtained which may be of value in detecting localised early hypertensive pulmonary vascular disease. Unfortunately, because of the short half-life of the isotope, studies must be performed in the close vicinity of a cyclotron. We are currently exploring the use of the more widely available isotope ^{133}Xe which has a much longer half-life but is more soluble than ^{13}N. It is probable that it will be possible to use ^{133}Xe but care will be needed to ensure that only a small dose is used if delayed clearance is anticipated because of this long half-life and slow biological clearance. The sensitivity and specificity of the technique are as yet uncertain but our preliminary results are encouraging. These studies may be particularly valuable for repeated

assessment of children with complicated cardiac defects in whom early hypertensive pulmonary vascular disease is a common complication, in order to determine the optimum time for corrective surgery.

We wish to thank our colleagues from the MRC Cyclotron Unit and the Department of Medical Physics for their wholehearted support which makes these investigations in sick children possible.

References

Alderson, P. O., Boonvisut, S., McKnight, R. C., and Hartman, A. F. (1976). Pulmonary perfusion abnormalities and ventilation-perfusion imbalance in children after total repair of tetralogy of Fallot. *Circulation,* **53,** 332–337.

Allen, H. D., Anderson, R. C., Noren, G. R., and Moller, J. H. (1974). Postoperative follow-up of patients with ventricular septal defect. *Circulation,* **50,** 465–471.

Braunwald, N. S., Braunwald, E., and Morrow, A. G. (1962). The effects of surgical abolition of left to right shunts on the pulmonary vascular dynamics of patients with pulmonary hypertension. *Circulation,* **26,** 1270–1278.

Cartmill, T. B., DuShane, J. W., McGoon, D. C., and Kirklin, J. W. (1966). Results of repair of ventricular septal defect. *Journal of Thoracic and Cardiovascular Surgery,* **52,** 486–499.

Damman, J. F., and Ferencz, C. (1956). The significance of the pulmonary vascular bed in congenital heart disease. *American Heart Journal,* **52,** 210–231.

Ellison, L. T., Hall, D. P., Yeh, T., Mobarhan, H., Rossi, J., and Ellison, R. G. (1961). Physiological alterations in increased pulmonary blood flow with and without pulmonary hypertension. *Journal of Applied Physiology,* **16,** 305–308.

Espino-Vela, J., Cardenas, N., and Cruz, R. (1968). Patent ductus arteriosus. With special reference to patients with pulmonary hypertension. *Circulation,* **37-38,** Suppl. V, V-45–60.

Godfrey, S., Ronchetti, R., Stocks, J., and Hallidie-Smith, K. (1975). Generalised pulmonary hyperinflation and Fallot's Tetralogy in a neonate investigated by pulmonary physiological and radioisotopic methods. *Thorax,* **30,** 452–460.

Grossman, W. (1974). *Cardiac Catheterization and Angiography.* Lea and Febiger, Philadelphia.

Kentera, D., Wallace, C. R., Hamilton, W. F., and Ellison, L. T. (1965). Venous admixture in dogs with chronic pulmonary hypertension. *Journal of Applied Physiology,* **20,** 919–921.

Kirklin, J. W. (1965). Ventricular septal defect with pulmonary vascular disease. *New Zealand Medical Journal* (Cardiac Suppl.), **64,** 34–36.

Lees, M. H., Way, R. C., and Ross, B. B. (1967). Ventilation and respiratory gas transfer of infants with increased pulmonary blood flow. *Pediatrics,* **40,** 259–271.

Maron, B. J., Redwood, D. R., Hirshfeld, J. W., Goldstein, R. E., Morrow, A. G., and Epstein, S. E. (1973). Postoperative assessment of patients with ventricular septal defect and pulmonary hypertension. Response to intense upright exercise. *Circulation,* **48,** 865–874.

Park, C. D., Nicodemus, H., Downes, J. J., Miller, W. W., and Waldhausen, J. A. (1969). Changes in pulmonary vascular resistance following closure of ventricular septal defects. *Circulation,* **39-40,** Suppl. I, I-193–200.

Ronchetti, R., Stocks, J., Freedman, N., Glass, H., and Godfrey, S. (1975). Clinical application of regional lung function studies in infants and small children using ^{13}N. *Archives of Disease in Childhood,* **50,** 595–603.

Wessel, H. U., Kezdi, P., and Cugell, D. W. (1964). Respiratory and cardiovascular function in patients with severe pulmonary hypertension. *Circulation,* **29,** 825–832.

Whitman, V., and Ellis, N. G. (1975). Pulmonary hemodynamics after repair of left to right shunt lesions associated with pulmonary artery hypertension. *Progress in Cardiovascular Diseases,* **17,** 467–473.

Winlove, P., Freedman, N., Fitzpatrick, M. L., and Godfrey S. (1976). The quantitation of regional lung function in infants and children using radioactive nitrogen (^{13}N). *(Submitted.)*

Wood, P. (1952). Pulmonary hypertension. *British Medical Bulletin,* **8,** 348–353.

Woolf, C. R. (1963). Pulmonary function in adults with intracardiac septal defect. *Circulation,* **27,** 261–267.

Requests for reprints to Dr. S. Godfrey, Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, Du Cane Road, London, W12 0HS.